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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/295,464	04/19/99	ONG	C 80135-0

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	10
DATE MAILED:	02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/295,464	ONG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6, 9, and 12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 9,and 12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 9 on 11/13/00. Claims 7, 8, 10, and 11 were canceled and claims 15-19 were added as requested. Claims 1-6, 9, and 12-19 are pending and under consideration in this office action.

Claim Objections

Claim 13 is objected to because of the following informalities: The word "cells" should be singular, not plural. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 13, 14, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of screening for integration of a DNA construct into a target gene having expression restricted to a specific eukaryotic tissue or specialized eukaryotic cell *in vitro* or *in vivo* in a mouse, wherein two DNA constructs encoding separate indicator components are integrated into the genome of the cell which is subsequently used to form a tissue or specialized cell in vitro, or to form a mouse, does not reasonably provide

enablement for a method in which either of the constructs is not integrated into the genome of a cell which must be replicated to form a tissue, specialized cell, or organism, and does not reasonably provide enablement for the production of any organism other than a mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-6, 13, 14, and 16-19 are directed to methods of screening for insertion of a DNA construct into a target gene having expression restricted to a specific eukaryotic tissue or specialized eukaryotic cell. The method requires the insertion of two separate DNA constructs into a cell of interest. The first construct comprises an indicator component under the control of a promoter having activity restricted to a specific eukaryotic tissue or specialized eukaryotic cell. The claims do not require integration of this construct into the cell's genome. The second construct encodes a second indicator component which is not linked to a promoter. This construct must be integrated into the cell's genome. The construct may be operably linked to an IRES or to a splice acceptor site, thereby allowing translation of the indicator component following integration downstream of a promoter which can transcribe the integrated sequence in the cell. The method requires the production of tissue or specialized cells from the cell comprising the two DNA constructs. This method step encompasses the production of transgenic animals from an embryonic stem (ES) cell as well as a variety of *in vitro* applications requiring proliferation and/or differentiation of the original cell. In particular, claim 19 requires the production of a transgenic mouse or pig using ES cells modified according to the invention.

Integration of the second (promoter-less) construct into a target gene with expression restricted to the tissue or specialized cells in which the indicator component of the first DNA construct is also expressed is then detected. This is preferably done by detecting the interaction of the two indicator components. For example, if one construct encodes a lac Z ω fragment, and the other encodes the lac Z α fragment, one can screen for β-galactosidase activity. This allows the discovery of genes or promoters with tissue-specific expression.

The claims encompass methods in which the transfected cell must be replicated in order to form tissue, specialized cells, or an animal. However, the claims do not require that the first DNA construct must be stably integrated into the genome of the original cell, and the disclosed constructs lack any means of replication, and the specification fails to teach how the construct can be maintained in cells which must proliferate. One of skill in the art appreciates that a DNA construct which cannot be replicated will not be maintained in dividing cells. For these reasons one of skill in the art would have to perform undue experimentation in order to practice the invention in dividing cells without ensuring genomic integration of the first DNA construct.

The claims also encompass the production of transgenic animals in general, and claim 19 is specifically limited to the production of transgenic mice and pigs. The specification teaches an example of the transfer of the two DNA constructs into cells for the formation of transgenic animals. The example involves the process of selecting for integration of the two constructs into the genome of an ES cell. The selection process requires the expression of drug resistance markers on each insertion construct. As discussed in Paper No. 6, at the time of the invention,

this technology was well developed in the mouse, but had not yet been extended to other animal systems. See Mullins, cited in the previous office action. For this reason, one of skill in the art would have to perform undue experimentation in order to produce any non-mouse animal using the method of the invention.

Applicant argues that the current state of the art supports the use of ES cells from pigs, and cites US Patent 5,523,226 to Wheeler as support. Wheeler provides a working example of chimeric animals produced by injection of Meishan swine ES cells into Duroc swine embryos, and injection of Duroc ES cells into Meishan embryos. Prophetic examples of genetic modification of the ES cells are described, but no working example of any selection procedure is disclosed. Thus, Wheeler fails to provide any evidence that pig ES cells were available at the time of the invention which could maintain totipotency after being subjected to transfection and drug selection. In support of this position Mullins acknowledged that, as of April, 1996, targeted gene replacement in pigs was not a reality due to the lack of suitable ES cells. See page S39, last sentence of first full paragraph. Thus, the assertion that non-mouse ES cells could be used to select targeted integration events is not supported by Wheeler or any other document of record, and undue experimentation would be required to perform the claimed invention using non-mouse ES cells. At the bottom of page 7 of Paper No. 9, Applicant also argues that it is routine in the art to make organisms from a wide variety of cells, and that this does not depend on the culturing of ES cells. It is unclear from this statement if Applicant is contending that transgenic organisms can be constructed from a wide variety of cells other than ES cells, or if Applicant is merely arguing that

although the production of transgenic animals from ES cells does not require selection steps. In any case, the specification fails to teach how to produce the transgenic animals of the invention without ES cells and without selecting for integration of the constructs. Furthermore, the contention that it is routine in the art to stably transfect and recover any cell with two independent constructs in the absence of any means of selection, and to subsequently use these cells to construct transgenic animals is not supported by evidence.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 15 recite the phrase "wherein the sequence encoding is not operably linked". The meaning of this phrase is unclear. It is suggested that the words "the enzyme subunit or fragment" should be inserted directly after the word "encoding" in claim 9, and the words "the inactive alpha or omega fragment" should be inserted directly after the word "encoding" in claim 15.

Claim 12 is unclear because it is unclear whether the second indicator component sequence should be, or should not be, linked to an IRES. It is suggested that a comma should be inserted after the phrase "transcriptional control element".

Conclusion

No claim is allowed.

All claims are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

Karen M. Hauda

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